Aetiology and outcome of neonatal cholestasis in Malaysia

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ABSTRACT

Introduction: Little is known about the epidemiology, causes and outcomes of neonatal cholestasis in the Asian population beyond Japan and Taiwan.

Methods: This was a prospective, observational study on patients with neonatal cholestasis who were referred to the University of Malaya Medical Centre, Malaysia, between November 1996 and May 2004.

Results: Biliary atresia (BA) (29 percent) and idiopathic neonatal hepatitis (38 percent) were the two commonest causes of neonatal cholestasis (n is 146) that were referred. Out of the 39 patients (27 percent of the total) who died at the time of review, 35 succumbed to end-stage liver disease. Three of the four patients (three BA, one progressive familial intrahepatic cholestasis [PFIC]) who had a living-related liver transplant (LT) died after the surgery (two BA, one PFIC). Six (four percent) of the remaining 107 survivors had liver cirrhosis. The overall four-year survival rates for patients with native liver and LT as well as those with native liver alone for all cases of neonatal cholestasis were 72 percent and 73 percent, respectively, while the respective survival rates for BA were 38 percent and 36 percent.

Conclusion: BA and idiopathic neonatal hepatitis are important causes of neonatal cholestasis in Malaysian infants. In Malaysia, the survival rate of patients with neonatal cholestasis, especially BA, is adversely affected by the lack of a timely LT.

Keywords: liver transplant, neonatal cholestasis, outcome

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INTRODUCTION

The causes of neonatal cholestasis are manifold.[1,2] Biliary atresia (BA) is the most commonly recognised cause of neonatal cholestasis throughout the world.[3-6] Other causes vary depending on the population studied. Among Caucasians, the three most common causes of neonatal cholestasis are BA, idiopathic neonatal hepatitis (INH) and alpha-1 antitrypsin (α1AT) deficiency.[3] Among Asians, α1AT deficiency is uncommon,[7-9] while citrin deficiency has recently been found to be a common cause of neonatal cholestasis with hepatic steatosis.[10,11]

Liver transplantation (LT) is the standard treatment for end-stage liver failure and fulminant liver failure in children.[12,13] In Europe and the United States, the results of paediatric LT have been excellent, with the majority of the liver grafts obtained from cadaveric donors.[12,13] In Asia, a severe lack of cadaveric grafts is a major problem that is faced throughout the region.[14] In order to overcome this problem, living-donor LT has been established in Japan, Taiwan, Hong Kong and Korea.[14]

LT is limited in Malaysia. It has only been made available in one private medical centre since 1995 and in one government hospital since 2002.[15] By the end of 2005, a total of 80 Malaysians had gone through an LT,[15] and out of these, only 16% had received their grafts from cadaveric donors.[15] The overall one-year survival rate was 69%.[15] Little is known about the epidemiology and outcomes of neonatal cholestasis in the Asian population beyond Japan and Taiwan. The objectives of the present study were to ascertain the epidemiology, the short-to-medium-term outcomes and the effect of limited LT on neonatal cholestasis in a single institution in Malaysia.

METHODS

This was a prospective, descriptive, non-interventional study conducted at the Department of Paediatrics, University of Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia. Infants with neonatal cholestasis who were referred to the department over the course of 7.5 years, between November 1996 and May 2004, were selected and studied. The inclusion criteria were infants born to Malaysian citizens, where adequate follow-up information was available for at least a period of four years and where a known final outcome was available. The present study was approved by the ethics committee of UMMC.

All patients with neonatal cholestasis were investigated according to a systematic protocol, which included a

Table I. Aetiology and outcomes of liver disease in 146 infants with neonatal cholestasis.

Underlying cause	No. (%)	Alive with minor or no residual morbidity	Alive with major morbidity*	Died
Bile duct obstruction				
Biliary atresia	42 (29)	14[a]	3	25
Definite (n = 35, 24%)				
Presumptive (n = 7, 5%)				
Choledochal cyst	1 (0.7)	1		
Alagille syndrome	1 (0.7)		1	
Caroli disease	1 (0.7)			1
Inspissated bile syndrome	1 (0.7)	1		
Neonatal hepatitis				
Idiopathic				
Idiopathic neonatal hepatitis	56 (38)	52	3	1
Viral				
Cytomegalovirus	13 (9)	12		1
Herpes simplex virus	2 (1.5)	2		
Bacterial				
Urinary tract infection	3 (2)	3		
Cholestatic syndromes				
PFIC	5 (4)		1	4
Endocrine				
Congenital adrenal hyperplasia	1 (0.7)	1		
Congenital hypothyroidism	3 (2)	3		
Congenital hypopituitarism	1 (0.7)	1		
Metabolic				
Galactosaemia	1 (0.7)	1		
Neonatal haemachromatosis	2 (1.5)			2
Acute liver failure, undefined	4 (3)	1		3
Toxic				
TPN-associated cholestasis	7 (5)	7		
Miscellaneous				
Perinatal asphyxia	2 (1.5)		2	
Total (%)	146 (100)	99 (68)	10 (7)	37 (25)

* The overall mortality rate of patients who presented with acute liver failure was 83% (5 out of 6).
[a] Includes two patients who survived after successful liver transplantation.
TPN: total parenteral nutrition; PFIC: progressive familial intrahepatic cholestasis

detailed history and physical examination, haematological, biochemical and serological investigations, imaging studies and percutaneous liver biopsy, where appropriate.[6] An operative cholangiography was performed if the outcome of the investigations was inconclusive and if BA was clinically suspected. A final diagnosis of neonatal cholestasis was made after careful consideration of all the available data.

Neonatal cholestasis was defined as the onset of clinically apparent jaundice within the first four months of life, with a conjugated bilirubin level > 17 µmol/L (1 mg/dL) if the total bilirubin level was < 85 µmol/L (5 mg/dL), or a conjugated bilirubin level > 20% of the total bilirubin level if the total bilirubin level was > 85 µmol/L.[16] BA was diagnosed based on the criteria identified by McKiernan et al[17] and Fischler et al,[18] when other causes of neonatal cholestasis were excluded and confirmation was obtained at laparotomy with an operative cholangiogram.[17,18] BA was considered to be definitive when laparotomy confirmed the obliteration of extrahepatic bile ducts, and presumptive when there was a consistent clinical feature and a natural course of progressive jaundice, eventual liver cirrhosis and death due to liver failure, but without confirmation by operative cholangiogram.

The diagnosis of progressive familial intrahepatic cholestasis (PFIC) was based on the presence of the following features: chronic unremitting cholestasis with onset in infancy, the exclusion of anatomic and metabolic aetiologies, raised levels of conjugated bilirubin and alkaline phosphatase and low to normal levels of serum gamma-glutamyl transferase (γGT).[19] A positive family history was necessary if γGT was not low.[20] α1AT deficiency was diagnosed by performing serum α1AT levels and phenotypes. An infant was considered to have INH after a thorough history, physical examination and

Table II. Morbidity and mortality in 146 patients with neonatal cholestasis.

Condition	Morbidity (n = 9)	Cause of death (n = 39)
Biliary atresia	Liver cirrhosis, n = 3	Without Kasai procedure, n = 12 After unsuccessful Kasai procedure, no LT, n = 12 After unsuccessful LT, n = 2
Idiopathic neonatal hepatitis	Liver cirrhosis, portal hypertension, bleeding oesophageal varices; n = 1 Hypersplenism and thrombocytopaenia, n = 1 (Down syndrome) developed acute myeloid leukaemia, n = 1	(Down syndrome): intractable heart failure due to large atrioventricular septal defect, n = 1
Progressive familial intra-hepatic cholestasis		Liver cirrhosis and liver failure, n = 4 Post-LT due to severe sepsis, n = 1
Acute neonatal liver failure (n = 6)		Acute liver failure, n = 5
Cytomegalovirus hepatitis		Liver cirrhosis and liver failure, n = 1
Caroli disease		Liver cirrhosis and intractable sepsis, n = 1
Alagille syndrome	Liver cirrhosis, failure to thrive, n = 1	
Perinatal asphyxia	Severe neurodevelopmental disabilities, n = 2	

LT: liver transplant

laboratory evaluations failed to identify the underlying cause of the neonatal cholestasis.[21]

A minimum of 48 months of follow-up data was available for all the patients. The age of death (months) for patients who died was noted. The outcomes of patients that were still alive were determined based on their clinical reviews. Basic clinical information, including growth parameters, general health, the presence of liver cirrhosis and its complications, daily and school activities, were noted. For patients who were still being followed up, the clinic entries nearest to June 2007, i.e. 48 months after the close of the study, were noted. For patients who had been discharged from the follow-up clinic, their latest clinical information was obtained from the care providers via telephonic interview.

The outcome measures were divided into the following: survival with or without minimal morbidity, survival with major morbidity and death. Major morbidity was defined as the presence of any of the following features: poor general health; major restrictions to lifestyle, including school activities; failure to thrive (minus two standard deviations for weight-for-age); the presence of liver cirrhosis or its complications and the need for LT. The Kasai procedure was considered to be successful if it resulted in the restoration of bile flow and normalisation of serum bilirubins (< 20 μmol/L) at any time.[17]

The data was entered using the Statistical Package for the Social Sciences version 11.0 (SPSS Inc, Chicago, IL, USA) for Windows XP. The data was quoted as the median and range. Chi-square tests were used for categorical data, while Student's *t*-test was used for a comparison of the numerical data.

RESULTS

During the study period, a total of 154 patients with neonatal cholestasis were referred to the department for further evaluation. Eight patients were excluded: the parents of two patients were non-Malaysian citizens with no outcome data, while another six patients had either incomplete investigations or inadequate follow-up. Hence, the remaining 146 patients were studied.

BA (n = 42, 29%; 35 definite, seven presumptive) was the commonest cause of neonatal cholestasis (Table I). Despite extensive investigations, the underlying cause of neonatal cholestasis could not be identified in 56 (38%) cases, and these were considered to have INH. Neonatal cholestasis and BA were mainly seen in term infants, with a median gestational age of 40 weeks for both neonatal cholestasis and BA. The median age of onset of jaundice for all the cases was seven (range 1–90) days, while the median age at referral was 58 (range 16–260) days. For BA, the median age of onset of jaundice was seven (range 1–75) days, while the median age at first presentation was 60 (range 16–260) days.

Six infants had Down syndrome (four for INH, one each for galactosaemia and congenital hypothyroidism).

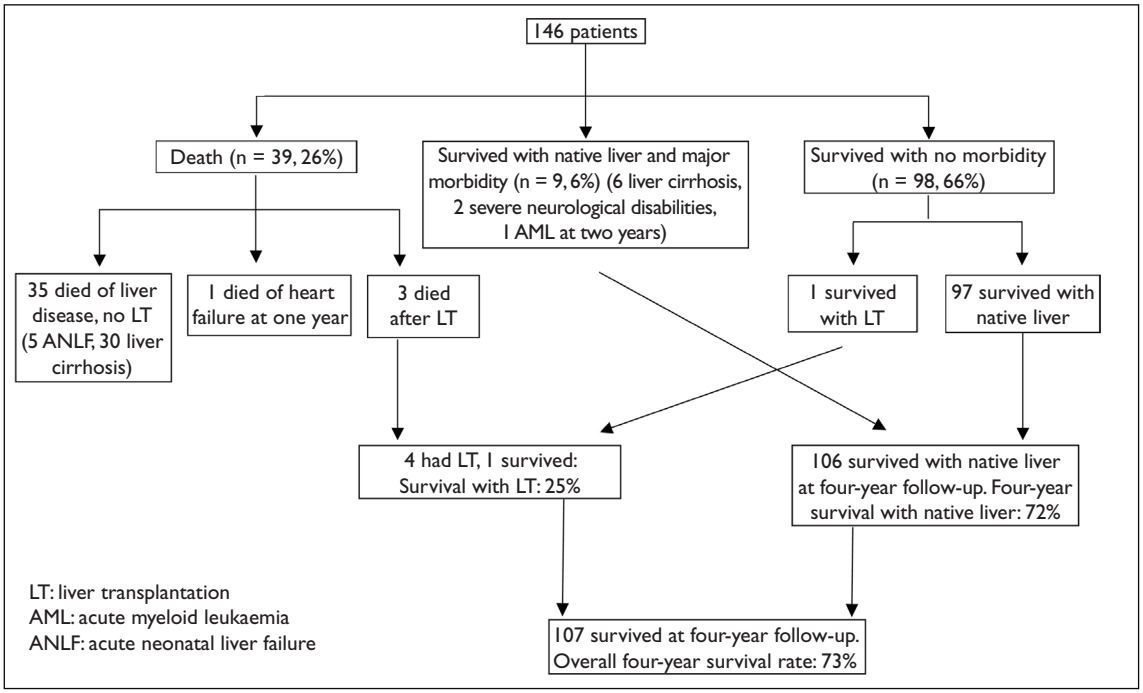

Fig. 1 Outcomes of 146 patients with neonatal cholestasis.

One patient with INH who had microcephaly and anal atresia at birth was subsequently diagnosed to have Kabuki syndrome at four years of age.

All the patients had a minimum of 48 months follow-up (Table II, Fig. 1). 39 (27% of the total) patients had died and 107 were still alive at the time of review in June 2008. Of the four patients who had LT, one is still alive with a functioning graft. The overall four-year survival rate of patients with native liver and LT, as well as those with native liver for all cases of neonatal cholestasis, was 72% and 73%, respectively.

Nine (6%) of the 107 survivors had major morbidity (Table II). Six patients had liver cirrhosis, portal hypertension and hypersplenism. One patient with Down syndrome, whose jaundice subsided at four months of age, developed acute myeloid leukaemia at two years of age. The patient responded well to chemotherapy and is currently in remission. Two patients with perinatal asphyxia survived with full recovery of the cholestatic jaundice, but had severe neurodevelopmental impairment. The remaining 98 (66%) patients survived with their native livers, with minimal or no morbidity. 48 of the 107 survivors were discharged from follow-up (median age 27 months, range 48–63 months). None had evidence of liver disease.

Of the 39 patients who succumbed (median age of death 14 months, range 1–51 months), the patient with Down syndrome and INH died of intractable heart failure, due to a large atrial septal defect unrelated to liver disease. Three of the four patients who had LT died after the LT. The remaining 35 patients died of end-stage liver disease. A total of six patients died acutely. Of these, five patients with acute neonatal liver failure (ANLF) died without LT (survival rate 17%). Another patient with PFIC died of a massive haemorrhage secondary to non-compliance of medical therapy. Of the five patients with PFIC, four patients who had both progressive liver cirrhosis and liver failure died without LT at 18, 22, 39 and 51 months of age, respectively. One patient died due to post-LT complications. The overall survival rate for PFIC was 0%.

Of the 42 patients with BA, all 12 patients who were referred late died without undergoing the Kasai procedure and LT (median age of death 15 months, range 6–18 months). Of the remaining 30 patients (71% of the 42 patients with BA) who underwent the Kasai procedure, 15 were unsuccessful (success rate for the Kasai procedure was 50%). Of these 15 patients, 12 died without LT (median age of death 15 months, range 8–25 months). Three patients with BA who had an unsuccessful Kasai procedure had LT, and only one is still alive with a functioning graft. For patients with BA, the overall four-year survival rate (native liver and LT, 16 out of 42) was 38%, while the four-year survival rate with native liver was 36% (15 out of 42).

Generally, patients with INH (n = 56, one died, mortality rate 2%) had a favourable outcome (Table I). One of the 13 patients with cytomegalovirus hepatitis died at 38 months of age due to progressive liver cirrhosis. Five of the six patients with ANLF died acutely without

LT. 29 patients with chronic liver failure died without LT. The parents of all these patients were counselled about the need for LT. Of these, only five explored the feasibility of LT; however, LT was not performed due to a lack of suitable living related donors. The parents of the remaining 24 patients declined the offer of LT. The main reasons for the decline were the prohibitively high cost (prior to 2002) and the possibility of the eventual failure of LT.

Of the four patients who had LT (three for BA, one for PFIC), all received a liver graft from a living-related donor (biological father or mother as donor, n = 2 each). The median age at LT was 15 (range 12–22) months. One patient who underwent an unsuccessful Kasai procedure died soon after LT due to a primary graft non-function. The second patient with PFIC died one week after LT due to severe sepsis. The third patient underwent LT for an unsuccessful Kasai procedure for BA and died three years after LT due to a chronic graft rejection. The remaining patient survived with functioning grafts ten years after LT.

DISCUSSION

The present study was conducted at a tertiary referral centre in Malaysia. It is likely that the cases of neonatal cholestasis that are reported in the present study represent the most severe of the cases, or those who required urgent attention. Only a population-based prospective study can determine the population incidence of the various causes of neonatal cholestasis.

BA and INH are the two most common causes of neonatal cholestasis that have been noted in Malaysia.[22] The percentage of patients with BA in the present study (29%) is similar to the figure of 38% noted by Karnameedi and Lim in a retrospective study conducted in the same institution.[22] However, unlike the previous study where all the other causes of neonatal cholestasis besides BA were classified as neonatal hepatitis, the present study identified various other causes of neonatal cholestasis.

The diagnosis of INH in the present study was certainly a diagnosis by default, as a diagnosis of INH is often made after excluding various infectious, metabolic, endocrine and anatomical causes of neonatal cholestasis.[23] In addition, the present study has also confirmed that α1AT deficiency-related liver disease is uncommon in the Malaysian population.[24,25]

The absence of LT adversely affects the outcomes of BA, ANLF and PFIC.[26-28] LT was mainly offered to chronic liver failure patients and not for ANLF. There is a severe lack of cadaveric liver grafts for the replacement of livers afflicted with end-stage liver failure, fulminant disease or inborn errors of metabolism.[14] This is particularly severe in Asian countries.[14] In the present study, 36 patients who died succumbed to liver failure. The limited availability of cadaveric donors for LT and the prohibitive cost of transplant surgery at a private centre in the early years of the study period were the main contributing factors to the high mortality rate observed in the present study. Only four patients underwent LT. Of the 36 patients who died, 34 died without LT. Another seven patients who survived showed evidence of liver cirrhosis and may require LT in the near future. Public campaigns to increase the number of cadaveric donors should be intensified in order to increase the availability of cadaveric grafts.

The outcome of BA is dependent on the timing of the Kasai procedure, the associated anomalies and the experience of the centre.[29,30] While the outcome of surgery for BA in the present study is comparable to that found in other studies, the overall outcome of BA, including for those who had an unsuccessful surgery, is not encouraging. The actuarial two-year survival rate with native liver was 36%, while the two-year actuarial overall survival rate with LT was 40%. The 36% survival rate with native liver is much lower than that observed in the results from the King's College Hospital study (five-year survival rate with native liver was 60%),[31] but comparable to figures from the French National Study (five-year survival rate with native liver was 32%),[30] as well as findings in Taiwan (five-year survival rate with native liver was 35%).[26]

The relatively unfavourable overall outcome for BA is mainly due to late referral for the appropriate investigations to be conducted.[32] The median age at referral for all cases of neonatal cholestasis was 58 days. We have previously argued that since there is a limited availability of LT in Malaysia, efforts to improve the outcome of BA should ideally address the issue of late referral.[32,33] Efforts should be made to increase awareness of the potentially serious nature of cholestatic jaundice in infancy among all levels of healthcare staff.[32] Mass screening of BA by checking the patients' stool colour, which has been conducted in Japan and Taiwan, should also be considered.[34,35]

In conclusion, the present study showed that the two major causes of neonatal cholestasis in Malaysia are BA and INH. The absence of timely LT adversely affects the outcomes of patients with BA, ANLF and PFIC who develop end-stage liver disease.

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